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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,734	07/28/2003	Jon A. Wolff	Mirus.013.03.6	5547

25032 7590 02/07/2007

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,734	WOLFF ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-21 and 23-34* is/are pending in the application.

4a) Of the above claim(s) *6-8,19-21 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 9-18, 23-27, and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 10/628,734 filed on July 28, 2003 is a CIP of 09/447,966 11/23/1999 PAT 6,627,616 which is a CIP of 09/391,260 09/07/1999 ABN, which is a DIV of 08/975,573 11/21/1997 PAT 6,265,387, which is a CON of 08/571,536 12/13/1995 ABN

Election/Restrictions

1. Applicant's election of Group I in the reply filed on February 7, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

With respect to the species election, Applicants elect the species of VEGF and skeletal muscle. Previous Examiner agreed with Applicants that the species recited in claim 5 are obvious variants of vascular endothelial cell growth factor, and is a well defined sub-genus of numerous characterized angiogenic factors known in the art at the time of filing. Accordingly, the restriction requirement is withdrawn to the extent it required a specific species of vascular endothelial cell growth factor recited in claim 5 to be elected. No arguments are provided for the species of muscle.

Claims 1, 2, 5-12, 23-34 are pending. Claims 3, 4, 22 and 35-38 are cancelled. Claims 6-8, 19-21, and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as

being drawn to a nonelected inventions and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 7, 2006. Claims 1, 2, 5, 9-18, 23-27, 29-34 are currently under consideration as they are drawn to a process for delivering a naked polynucleotide to a skeletal muscle of a patient.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of claims: Claims 1, 2, 5, 9-18, 23-27, 29-34 are currently under examination.

Petition of delayed benefit claim

2. Applicants' petition for acceptance of delayed benefit claim to the prior-filed applications under 37 CFR 1.78(a)(3), filed July 17, 2006, has been *granted.* Office of Petitions made the decision on Jan. 17, 2007. It was noted that "The granting of the petition of the petition to accept the delayed benefit claim to the prior-filed applications under 37 CFR 1.78(a)(3) should not be construed as meaning that the instant application is entitled to the benefit of the prior-filed applications. In order for the instant application to be entitled to the benefit of the prior-filed application, all other requirements under 35 U.S.C. § 120 and 37 CFR 1.78(a)(1) and (a)(2) must be met" (See first paragraph, page 2, decision of Office of Petition, Jan. 17, 2007).

Claim Objections

3. The previous objection of claim 1 under first paragraph of 35 U.S.C. 112 has been *withdrawn*. Applicant's arguments filed July. 17, 2006 have been fully considered and they are persuasive.

More specifically, Applicants amended claim 1 reciting "A process for delivering naked polynucleotides to a skeletal muscle tissue of a patient comprising: a) injecting the naked polynucleotides into a blood vessel lumen, *in vivo*, wherein the naked polynucleotides encode a vascular endothelial growth factor; b) increasing extravascular volume in the skeletal muscle tissue; and, c) delivering the naked polynucleotides to extravascular skeletal muscle cells via the increased volume, wherein the vascular endothelial growth factor is expressed from the polynucleotides resulting in improving blood flow in the tissue." Accordingly, amendments of claims dependent from claim 1 have been made.

The previous objection of claims 2, 5, 13, 14, 30, 31-34 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, has been *withdrawn*. Applicant's arguments filed July. 17, 2006 have been fully considered and they are persuasive. Appropriate amendment regarding dependency of claims has been made.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. The previous rejection of claims 1, 2, 5, 9-18, 23-27, and 29-34 under second paragraph of 35 U.S.C. 112 has been *withdrawn*. Applicant's arguments filed July. 17, 2006 have been fully considered and they are persuasive.

More specifically, Applicants amended claim 1 reciting "A process for delivering naked polynucleotides to a skeletal muscle tissue of a patient comprising: a) injecting the naked polynucleotides into a blood vessel lumen, *in vivo*, wherein the naked polynucleotides encode a vascular endothelial growth factor; b) increasing extravascular volume in the skeletal muscle tissue; and, c) delivering the naked polynucleotides to extravascular skeletal muscle cells via the increased volume, wherein the vascular endothelial growth factor is expressed from the polynucleotides resulting in improving blood flow in the tissue." Accordingly, amendments of claims dependent from claim 1 have been made.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The previous rejection of Claims 1, 2, 5, 9-18, 23-27, 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (US Patent 6,121,246) in view of Milas et al., Von Der

Leyen et al. and Budker et al. (each listed in the IDS), is *maintained* for the reasons of record advanced from pages 6-8 of the Non-Final Office action mailed on 04/17/2006.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) was acknowledged by previous examiner in the Non-Final Rejection mailed on 04/17/2006. It was noted that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.,* 38 F.3d 551, 32 USPQ2d 1077 fled. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/447,966, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Accordingly, the priority date given the instant application is it's filing date of July 28, 2003. Further elaboration in this regard is documented of the record as part of *Response to Applicants' Arguments* below.

Applicant's arguments filed July 17, 2006 have been fully considered and they are ***not*** persuasive. Specifically, applicants have amended claim 1 and filed a petition to grant delayed priority claim to Application No. 08/571,536, filed Dec. 13, 1995, to obviate the rejection. Claim 35 has been canceled. It is the Applicants' opinion that amended claim 1 contains

adequate support in the priority documents. In view of the amendment and the priority claim, Applicants request reconsideration of the rejection.

Response to Applicants' Arguments

As indicated in the section regarding priority date of instant application, it is determined that the prior-filed application 09/447,966 (Monahan et al., U.S. Patent No: 6,627,616, issued on Sep. 30, 2003) does not support the amended claims of instant application regarding (i) naked polynucleotides encode a ***vascular endothelial growth factor***, and (ii) the vascular endothelial growth factor is expressed from the polynucleotides ***resulting in improving blood flow*** in the tissue.

It is noted that the instant application is a CIP of prior-filed application 09/447,966 and the prior-filed application 09/447,966 only provides support for either delivering naked ***polynucleotides*** (See claim 1, Monahan et al., 2003), or, in a different context, a biological active protein molecule affecting permeability of the blood vessel being a vascular endothelial growth factor (VEGF) (See lines 38-54, column 7, Monahan et al., 2003). Accordingly, the "polynucleotides" taught by Monahan et al., 2003 is a genus whereas the amended claim 1 of instant application reciting the "polynucleotides encode a vascular endothelial growth factor" is a species. A genus does not anticipate a species, and thereby, prior-filed application 09/447,966 does not have proper support for the claims of instant application.

Regarding the limitation "the vascular endothelial growth factor is expressed from the polynucleotides resulting in improving blood flow in the tissue" recited in claim 1 of instant application, the prior-filed application 09/447,966 only provides support for the definition of

afferent blood vessels (bloods flows toward the organ) and efferent blood vessel (bloods flows away the organ) (See lines 33-38, column 3, Monahan et al., 2003). Relevant to this issue, it is worth noting that the term "improving blood flow" is literally supported by the instant application (See original claim 1 of instant application). However, the term "improving blood flow" encompasses changes of various biophysical parameters (for instance, kinetics and thermodynamics) related to the blood flow in the tissue, which is not supported by the instant application.

In summary, the previous rejection of Claims 1, 2, 5, 9-18, 23-27, 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (US Patent 6,121,246) in view of Milas et al., Von Der Leyen et al. and Budker et al. (each listed in the IDS), is *maintained* for the reasons of record advanced from pages 6-8 of the Non-Final Office action mailed on 04/17/2006.

For completeness of this office action, below is the recitation of pages 6-8 of the Non-Final Office action mailed on 04/17/2006.

The invention encompasses a process for delivering an angiogenic protein or peptide wherein the angiogenic protein is a vascular endothelial growth factor to a skeletal muscle to enhance blood flow, comprising administering a naked polynucleotide to a blood vessel that encodes an angiogenic protein, increasing the pressure in and delivering the nucleic acid to the skeletal muscle. At the time of filing gene therapy methods for the treatment of ischemic tissue were known and practiced. Isner discloses gene therapy methods where a polynucleotide encoding an angiogenic factor is delivered to ischemic muscle tissue. More specifically, Isner discloses the delivery of a polynucleotide encoding various species of VEGF (VEGFI65 in EXAMPLE 1 for example) to the muscle of a subject to induce angiogenesis. Upon analysis it

was found that the treatment resulted in new capillary formation as expected (see column 8 for example). Isner discusses the general use of the method for a variety of circumstances in which ischemic tissue results, including results of disorders, disease or damage (see column 2 for example or summary in abstract). Isner discloses that a variety of methods for delivery are known and can be used, and would depend in particular on the specific requirements of treatment (starting at the bottom of column 5 for determining effective amount, and more generally throughout columns 1-6). Isner discloses a variety of methods for delivery, including the delivery and expression in a vessel, however fails to specifically teach a delivery method to the muscle by increasing the extracellular volume during delivery. At the time of filing, each Milas et al., Von Der Leyen et al. and Budker et al. provide methodology and working examples where pressure mediated delivery was used to deliver DNA to skeletal muscle, and the demonstration that expression of the DNA was accomplished (Milas et al. and Budker et al.).

Isner teaches a variety of methods for delivery and how they would be dependent on what was being treated, and in particular the problems of delivery through a vessel with a catheter. Milas et al., Von Der Leyen et al. and Budker et al. each provide a teaching that the methods disclosed worked and have clinical merit, therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the teaching of Milas et al., Von Der Leyen et al. and Budker et al. for methods of delivery of a polynucleotide to a subject in conjunction with the teaching of Isner to more effectively deliver and affect angiogenesis in a subject in need thereof. One having ordinary skill in the art would have been motivated to use the methods of Milas et al., Von Der Leyen et al. and Budker et al. for delivery to the muscle. Based on their own results, Von Der Leyen et al. specifically proposes the use of

the methodology for the vascular gene therapy (page 2363). Based on the results of Isner, there would have been a reasonable expectation of success that VEGF would induce angiogenesis, and that the methods of Milas et al., Von Der Leyen et al. and Budker et al. would be effective in the delivery of a polynucleotide to skeletal muscle.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

7. No claim is allowed.

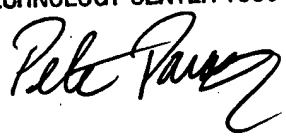
Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600



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Patent Examiner
Art Unit 1632